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Research Article

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A Possible Role for H. Pylori Eradication Therapy as Adjuvant Therapeutic Modality for Non-Herpetic Recurrent Aphthous Stomatitis

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ABSTRACT

Objectives : To evaluate coincidence between Helicobacter pylori (Hp) infection and non-herpetic recurrent aphthous stomatitis (NH-RAS), and the effect of its eradication on ulcer severity as guided by the Ulcer Severity Score (USS). Patients & methods : 115 NH-RAS patients free of dyspeptic manifestations were clinically evaluated, and then underwent Hp stool antigen test (Hp-SAT). The patients who gave negative Hp-SAT result were prescribed the conventional oral ulcer therapy for 1-m duration, and then were re-examined for clinical status and USS (Control group), and the patients who gave positive Hp-SAT result were prescribed the Hp triple therapy for 14-days and conventional oral ulcer therapy for 1-m duration, and then were re-examined for clinical status and USS. Hp-SAT was repeated 1-m after the end of the triple therapy course.Results : Hp-SAT test was negative in 81, and positive in 34 patients. Repeated Hp-SAT was negative in 25 patients (Responders), and still positive (Non-responders) in 9 patients. Baseline USS was significantly (p=0.032) higher in Hp positive than negative patients. The 1-m USS of control patients was non-significantly lower than their baseline USS, while it was significantly lower (p=0.001) in study patients compared to both their baseline score and 1-m USS of controls (p=0.005). The 1-m USS of responders was significantly (p=0.001) lower compared both to their baseline USS and 1-m USS of non-responders and Hp negative patients. In non-responders, 1-m USS was significantly (p=0.044) lower compared to their baseline USS with non-significant difference versus Hp negative patients. Conclusion : Hp infection may predispose to recurrence of NH-RAS and induce aggravation of clinical manifestations. Hp eradication therapy in conjunction with conventional RAS therapy helps significant reduction of manifestations. Hp-SAT may be incorporated with investigations underwent by RAS patients as it is a safe, easy and reliable test.

Key words: *Non-Herpetic Recurrent Aphthous Stomatitis, H. Pylori Infection, Ulcer Severity Score, H. Pylori Stool Antigen Detection Test.*

INTRODUCTION

Aphthous stomatitis is one of the most common ulcerative diseases of oral mucosa [1]. It is characterized by being painful, recurrent single/multiple, shallow, round or ovoid mucosal ulcerations which are slow to heal [2]. Moreover, it may interfere speech, eating and thus affecting patients' daily activities and wellbeing [3].

Recurrent Aphthous Stomatitis (RAS) is defined as multifactor immunologic inflammatory oral cavity lesions [2]. It is prevalent in developed countries, occurring in all ages, geographic regions and races, and about 80% of people have at least one episode of oral aphthous ulcers before the age of 30 [4]. RAS is characterized by the presence of erosions/ulcerations, ulcerations with necrosis or erythematous halo underlying the mucous membrane lining [5].

Etiology of RAS is not yet completely clear ; however, several local, systemic, immunologic, genetic, allergic factors, as well as immunosuppressive drugs may play a role in its pathogenesis [6]. Oxidative stress and lipid peroxidation associated with the imbalance of the trace elements may have a role in RAS pathogenesis [7]. Also,

food allergies, hormonal disorders, some viral and bacterial infections, mechanical injuries and stress may modify immunologic response in RAS [8].

The Gram-negative Epsilon proteo-bacterium Hp is one of the major human pathogens with varied virulence mechanisms and genomic diversity [9]. Hp developed mechanisms neutralize the effects of acidic pH, so it is well adapted to colonize the epithelial surface of the human gastric mucosa, and can cause persistent infections [10]. Some recent studies commented on the presence of Hp bacterium in food, water and oral cavity with a documented intra-familial spread which can be considered as an important mode of Hp transmission [10, 11].

Oral cavity was considered as an important reservoir for Hp bacteria [12] aside and independent from the stomach [13]. There was high prevalence of Hp in dental plaque [12] and correlations were detected between oral cavity Hp infection and periodontal diseases, oral tissue inflammations, Hp transmissions, and gastric reinfections [14], with the presence of halitosis, Decayed, Missing, Filled index, and oral pH [13].[31] extensively reviewed the antitumerigenic, antithrombotic, antiviral, antidiabetic, antioxidant activities and anticariogenic, antifungal activities, and effects on periodontal disease, and halitosis in the oral cavity. And, multiple studies found that Hp is found more often in patients with poor oral hygiene, and recommended oral sanitation and good hygiene as a positive contributor to eradication therapy [12, 15, 16]. Also, Salivary fluid has been considered as an important physiologic fluid and a diagnostic agent. Saliva fluid in the mouth protects dental caries, erosion, scraping and periodontal diseases [30].

Hypothesis

Co-infection by Hp bacteria may play a determinant role in outcome of treating oral ulcer, and may be responsible for recurrence or resistance to treatment.

Objectives

The current study targeted to evaluate the coincidence between Hp infection and non-herpetic RAS (NH-RAS), and the impact of Hp eradication on severity of RAS as guided by the Ulcer Severity Score (USS).

Setting

University Hospital, Cairo, Egypt

Design

Double-blinded prospective comparative clinical trial was used in the current study.

PATIENTS AND METHODS

The study intended to include NH-RAS patients referring to outpatient clinics of Dermatology, Otorhinolaryngology and General Medicine. To assure the diagnosis of NH-RAS, herpetic ulcers were excluded by HSV-IgM test. Also, patients with acute traumatic, or malignant ulcers, or Lichen planus were excluded from the study. Patients with peptic ulcer, gastro-esophageal reflux, inflammatory bowel diseases, immunological disorders, immunosuppressive diseases, or on immunosuppressive therapy or peptic ulcer therapy were also excluded from the study. The study protocol was approved by the Local Ethical Committee, and all the enrolled patients signed written fully informed consent for study participation and receiving assigned therapies.

All the patients were evaluated for demographic data including age, gender and body mass index (BMI), history of predisposing factors as tobacco smoking, hormonal disturbances, nutritional deficiencies, stress factors, associated drug intake, food hypersensitivity, and family history for similar lesions.

The ulcers were examined and classified morphologically as small ulcers (minor-type) if they were 2-5 mm in diameter, large ulcers (major-type) if they were 1–3 cm in diameter, and deeply indurated or Herpetiform aphthous ulcers if appeared as grouped lesions of very small ulcers of 1–2 mm in diameter [17]. Then, the ulcers were classified based on the time course as simple RAS which was presented as a limited number of small, quickly healing, minimally painful ulcers limited to the oral mucosa and recurring with 3–6 episodes annually, or complex RAS which was presented as few or many slowly healing, repeatedly recurrent ulcers within short ulcer-free duration (UFD), intensely painful ulcers interfering eating, and resulting in problems of inadequate nutrition [18].

Clinically all the patients were evaluated using the Ulcer Severity Score (USS)[19] that evaluates 6 parameters; the number was scored by one for each ulcer/crop with a maximum score of 20 for the patient who had >10 ulcers/crop, size as identified by patient in comparison to the list of rings of varied diameters, and was scored by one for each 1-mm diameter for a maximum score of 20 for collective size of >10 mm in diameter; the duration was scored by one for each half-week duration unit for a maximum score of 10 for ulcer lasting for ≥5 weeks; ulcer-free duration

(UFD) was scored as 10 minus the UFD in weeks; the pain was scored from one which indicates slight discomfort to 10 if the pain is severe and interfering sleeping, eating and talking; the 6th parameter is the site of the ulcer which was scored by one for each site on non-keratinized mucosa including, labial mucosa, buccal mucosa, buccal sulcus, soft palate, ventral of tongue or floor of mouth, and two for each site on keratinized or specialized mucosa including hard palate, attached gingival, alveolar ridge, dorsum of the tongue, tonsils, pillars of fauces, uvula, or oropharynx with a maximum score of 10. Total score was calculated as the summation of the scores of the six parameters, and determined on the 1st visit, and at the end of 1-m treatment.

H. pylori diagnosis

All patients gave fresh stool specimens for testing H. pylori stool antigen. H. pylori stool antigen test (Hp-SAT) was performed using OneStep H. pylori Antigen RapiCardTM Insta Test (Cortez Diagnostics, Inc, Califa St, Woodland Hills, California, USA) according to the manufacturer's instructions. Briefly, small stool specimens were collected from three different parts of the stool sample, vigorously shacked in a vial with diluent, allowed to sediment for two minutes, and then 2-3 drops of supernatant were put into the sample well of the test cassette. If the sample contained H. pylori antigens, it would bind to the antibody coated on red colloidal gold particles to form antigen-antibody-gold complexes which move on the nitrocellulose membrane by capillary action toward the test line region (T region) on which H. pylori specific antibodies were immobilized. A second red control line would always appear in C region to indicate that the test has been correctly performed and the test device functioned properly. Appearance of two red lines at T and C regions indicated that the test was positive, i.e. H. pylori antigen was present. Appearance of red line in C region only indicated negative test, but if no color appeared at C region, the test was considered as invalid.

Patients' grouping

Enrolled patients were categorized according to the results of Hp infection detection tests into two groups :

1. Control group included patients who gave negative result on Hp-SAT and were prescribed the conventional oral ulcer therapy for 1-m duration, and then re-examined for clinical status and USS.
2. Study group included patients who gave positive result on Hp-SAT, and were prescribed the Hp triple therapy for 14-days and conventional oral ulcer therapy for 1-m duration, and then re-examined for clinical status and USS. Hp-SAT was repeated 1-m after the end of the triple therapy course.

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers and ratios. The results were analyzed using paired t-test and One-way ANOVA with post-hoc Tukey HSD Test. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015) for Windows statistical package. P value <0.05 was considered statistically significant.

RESULTS

The study included 136 patients eligible for evaluation; 21 patients were excluded and 115 RAS patients showed no definite response on previously received conventional RAS therapy, were free of dyspeptic manifestations, and never received Hp treatment were enrolled (Fig. 1). Demographic and general clinical data of the enrolled patients are shown in table 1. Clinical evaluation of enrolled patients detected minor-type RAS in 69 patients, major-type RAS in 29 patients, and Herpetiform RAS in 17 patients. Ninety-four patients had simple RAS, and 21 patients had complex RAS ; 13 had minor-type, 6 had major-type and two had Herpetiform RAS (Fig. 1).

Baseline total USS determined at the time of enrolment was significantly lower in patients with minor-type RAS compared to the patients of major-type and Herpetiform RAS (p=0.001) and non-significantly lower USS in patients with Herpetiform than major-type RAS (p=0.763). Also, baseline total USS was significantly (p=0.001) lower in the patients with simple than the patients with complex ulcer (Fig. 2).

Eighty-one patients gave negative, while 34 patients gave positive Hp-SAT ; 26 patients had simple and 8 patients had complex RAS. Also, 17 patients were with RAS of minor type, 9 patients were with RAS of major type and 8 patients were with Herpetiform RAS, and gave positive Hp-SAT.

All patients who gave positive Hp-SAT, received the triple H. pylori eradication therapy for 14 days, and Hp-SAT was repeated 1-m after completion of therapy. Twenty-five patients became negative (Responders), while 9 patients were still positive (Non-responders). According to the morphological appearance of RAS at baseline time, 13 responders had minor RAS (52%), 7 responders had major RAS (28%) and 5 responders had herpetiform RAS (20%). Clinically, 21 responders (84%) had baseline simple RAS, while only 4 responders had baseline complex RAS (Fig. 3).

Table 1. Patients' enrolment data

Data		Findings
Age (years)		36.7±10.9
Gender	Males	32 (27.8%)
	Females	72 (72.2%)
Body mass index data	Body weight (kg)	88.8±7.4
	Body height (cm)	169.5±3.3
	Body mass index (kg/m^2)	30.9±2.3
Family history of RAS	Yes	19 (16.5%)
	No	96 (83.5%)
History of food allergy	Yes	11 (9.6%)
	No	104 (90.4%)
Hormonal disturbances	Yes	29 (25.2%)
	No	86 (74.8%)
Smoking	Non	56 (48.7%)
	Current	33 (28.7%)
	Ex-smokers	26 (22.6%)
History of physical or psychological stress	Yes	43 (37.4%)
	No	86 (62.6%)

Data are presented as mean±SD, numbers ; percentages are in parenthesis

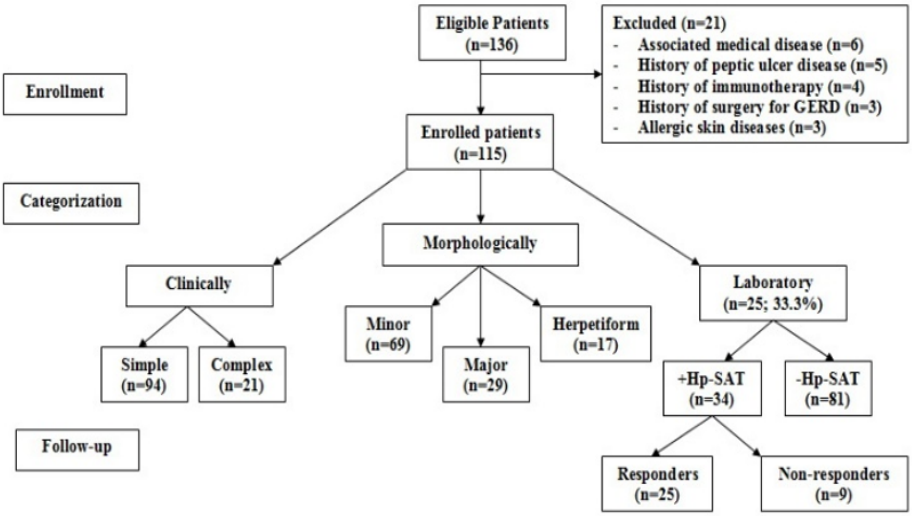

Figure 1. Flow chart of the study

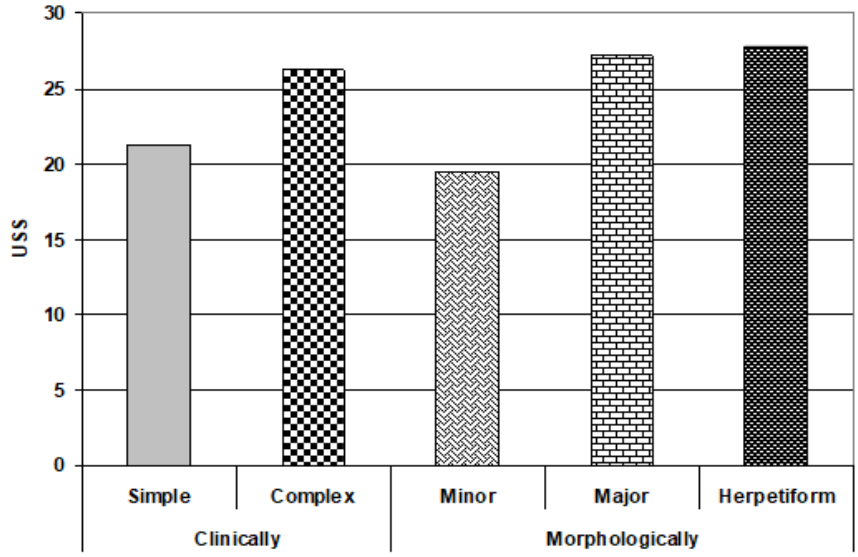

Figure 2. Mean baseline USS of studied patients categorized according to morphological and clinical types of ulcer

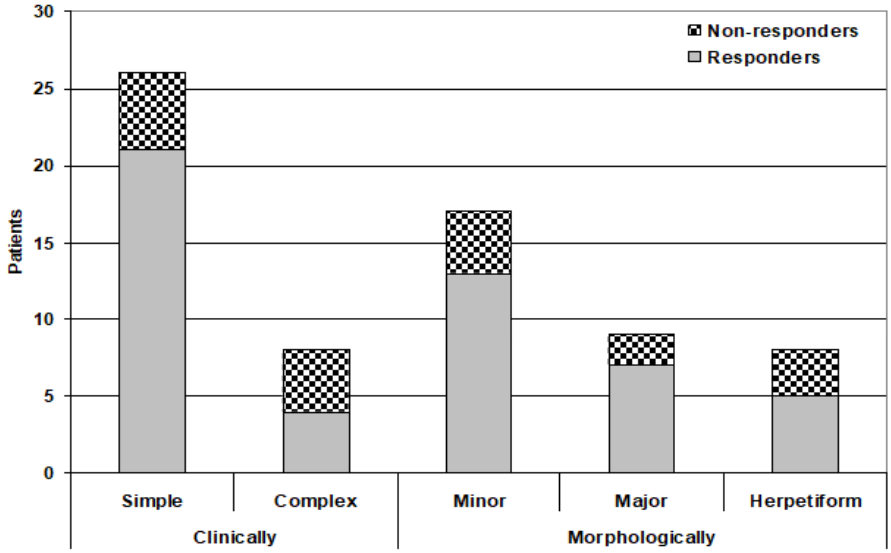

Figure 3. Hp-positive patients distribution according to RAS clinical and morphological types among responders and non-responders to Hp eradication therapy

Mean baseline USS of Hp positive patients was significantly (p=0.032) higher than Hp negative patients. USS determined at 1-m after treatment was non-significantly (p=0.074) lower in Hp patients compared to their baseline USS. On the other hand, USS determined at 1-m after treatment was significantly lower in HPpositive patients compared to their baseline USS (p=0.001), and the 1-m USS of Hp negative patients (p=0.005). Despite the non-significant difference between baseline USS of HP negative, Hp positive responders and non-responders; the 1-m USS of responders was significantly (p=0.001) lower compared to their baseline USS and to the 1-m USS of Hp negative patients and non-responders to Hp treatment. However, 1-m USS score of non-responders was significantly (p=0.044) lower compared to their baseline USS with non-significant (p=0.777) difference versus Hp negative patients (Table 2).

Table 2. Patients' clinical data determined at 1-m after treatment compared to baseline data

Patients		Baseline USS	1-m USS	P value
Hp-negative patients (n=81)		21.5±7.7	19±10	0.074
Hp-positive patients	Responders (n=25)	22.5±6.7	11.1±5.4	0.001
		P1=0.561	P1=0.001	
	Non-responders (n=9)	27.9±9	20±6.1	0.044
		P1=0.053 P2=0.069	P1=0.777 P2=0.001	
	Total Hp-positive patients (n=34)	25.1±9.4	13.7±7.1	0.001
		P1=0.032	P1=0.005	
Total patients		22.2±7.7	17.4±9.4	0.001

Data were presented as mean±SD, P value indicated significance of difference between baseline and 1-m USS, P1 value indicated significance of difference between Hp-negative patients ; P2 value indicated significance of difference between responders and non-responders to Hp eradication therapy

DISCUSSION

Screening of studied NH-RAS patients free of dyspeptic manifestations, for H. pylori infection relying on H. pylori stool antigen test (Hp-SAT) detected 34 stool specimens positive and 81 specimens negative for Hp-SAT. The studied NH-RAS patients who showed no definite response on previously received conventional NH-RAS therapy, were free of dyspeptic manifestations, never received treatment for Hp, and fulfilled exclusion criteria for the current study ; thus the reported positive Hp-SAT indicated a possibility for presence of hidden Hp infection in NH-RAS patients, and this may play a role in chronicity and recurrence of NH-RAS despite the repeated courses of conventional therapy.

The reliance on Hp-SAT to detect hidden Hp infection went in hand with Kalach et al.[20] who found that the Hp-SAT showed sensitivity and specificity rates of 91.3% and 97%, respectively with an accuracy rate of 96.2%, and concluded that Hp-SAT is consistent, reliable, quick and specific test for detecting Hp infection. In support of the applied diagnostic policy, Diaconu et al.[21] documented that UBT and Hp-SAT can be used to confirm Hp infection eradication, and should be performed at least 4 weeks after the completion of therapy.

Li et al.[22]in a meta-analysis of seven case-control studies detected a frequency Hp infection of 29.5% among RAS patients versus 20% in non-RAS controls, and concluded that Hp infection is associated with an increased risk of RAS. Also, Ding et al.[23] reported that oral Hp infection is common in adult patients, and is significantly associated with oral diseases including RAS. Moreover, Gülseren et al. [24]evaluated the hypothesis that Hp infection and periodontal diseases might play an etiological role in RAS, and detected significantly higher frequency of positive RUT test in RAS patients versus controls (89.5% vs. 55.8%), and documented that Hp plays a role in the development of RAS, but periodontal diseases have no effect on it. Gomes et al.[25] out of review of literature, documented that using varied diagnostic modalities, Hp infection can be detected in oral mucosa or ulcerated lesion of some patients with RAS.

In support of the relationship between H. pylori and RAS, Irani et al.[26]studied 228 biopsies of varied oral lesions and detected a significant difference between the frequency of Hp positivity in normal tissues, and examined lesions with significant differences between Hp positivity in different tissue types with significantly higher positivity in epithelium and lamina propria, then inside the blood vessels and lastly inside the salivary gland duct. Also, Lauritano et al. [27] documented that the histological detection of Hp in RAS ulcers supported the idea of a correlation between the two diseases, and the high incidence of anemia in patients with RAS may be caused by Hp-positive stomach disease.

All of the Hp-positive RAS patients (n=34) received combined H. pylori eradication therapy and conventional anti-RAS therapy for three months, and 25 patients (73.5%) became Hp-negative (Responders), and fortunately showed significantly lower USS compared to their baseline USS and to the 3-m USS of both the Non-responders, and Hp-negative RAS patients who received only conventional anti-RAS therapy.

These findings went in hand with Gülseren et al.[24]who documented that eradicating Hp might be useful to prevent RAS, and Gomes et al.[25] who also concluded that Hp eradication may affect the clinical course of the oral lesions by undetermined mechanisms. In a similar comparative study, Taş et al.[28] reported that the mean number of aphthous lesions per 6 months was significantly decreased after Hp eradication, while in the non-eradicated patients, no significant change was found, and concluded that Hp eradication in RAS-patients has beneficial effects.

In trial to explore the underlying mechanisms for the relation between RAS and Hpinfection, Yakar et al.[29] investigated whether Hp infection causes or triggers RAS, and found RAS patients with Hp gastritis showed a significantly higher frequency of GC IL-6 genotype than RAS patients without Hp gastritis (52 vs. 11%), and RAS patients with Hp gastritis showed a significantly lower serum cobalamin levels than non-RAS patients with Hpgastritis.

CONCLUSION

H. pylori infection may predispose the recurrence of aphthus stomatitis, and induce the aggravation of clinical manifestations. Hp eradication therapy in conjunction with conventional RAS therapy helps significant reduction of manifestations. Hp stool antigen detection test may be incorporated with investigations underwent by RAS patients as it is a safe, easy and reliable test. Further studies are needed to be done to confirm the exact mechanism underlying the ulcer healing and identify the chemical constituents responsible for it [32]. Therefore, wider scale study with longer follow-up duration is mandatory for confirmation of these results.

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